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**RADIATION EFFECTS IN MAN: MANIFESTATIONS
AND THERAPEUTIC EFFORTS**

REPORT PERIOD

May 1, 1967 through April 30, 1968

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**HEADQUARTERS
DEFENSE ATOMIC SUPPORT AGENCY
WASHINGTON, D.C. 20305**

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PREPARING AGENCY

University of Cincinnati College of Medicine
Cincinnati General Hospital
Cincinnati, Ohio 45229

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Foreword

This report was prepared by the following members of the University of Cincinnati College of Medicine:

Eugene L. Saenger, M.D.

Ben I. Friedman, M.D.

Harry Horwitz, M.D.

James G. Kereiakes, Ph.D.

The research was supported by the Medical Division, Defense Atomic Support Agency, Washington, D.C. The Project Officer for the contract is Lt. Robert L. Bonsanti.

These studies were performed in conformation with the "recommendations guiding doctors in clinical research" as stated in the Declaration of Helsinki of the World Medical Association (1964).

Research was conducted according to the principles enunciated in the "Guide For Laboratory Animal Facilities and Care", prepared by the National Academy of Sciences - National Research Council.

Introduction

This report summarizes only the work of the past year without detailed reference to previous efforts of this project. The last report, DASA 1844, summarized our total effort from February 1960 through April 30, 1966. Other earlier reports include DASA 1422 and DASA 1633 which may be consulted.

In this report there are included biochemical studies of deoxycytidine, immunology, psychological and psychiatric factors, clinical observation of autologous marrow infusion and computer analysis of hematological data.

The aims and design of the study insofar as human beings are concerned have not changed since the previous report. There is no change in dosimetry.

Several of us have had the opportunity to collaborate in the management of several cases of accidental "whole" and partial body irradiation in civilian accidents, the most notable of which was the overexposure of three individuals at the Gulf Research Corporation in Pittsburgh on October 4, 1967. Some of the information from these experiences will be reflected in this report.

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I. Biochemical Studies

A. Colorimetric technique for assaying deoxycytidine (CdR) in urine (1).

In this assay, deoxycytidine was isolated from urine by a combined use of cation and anion exchange columns. The isolated deoxycytidine was hydrolyzed and treated with periodate. The resulting malonaldehyde was reacted with thiobarbituric acid to form pink chromogen. By the use of this colorimetric assay, it was possible to detect as little as 1.0 ug of CdR per 10 ml of urine.

B. Dose-response study in rats. The analytical technique described above was used to assay CdR levels in the urines of rats x-irradiated at various whole body exposures from 25R up to 800R. In all exposure groups, the CdR levels increased during the first day post-irradiation and then decreased to the pre-irradiation levels during the second and third day post-irradiation. The quantity of CdR excreted was proportional to the exposure doses up to 200R and then reached a plateau. Approximately, a six-fold increase from an average pre-irradiation value of 0.7 mg per 24 hour urine was attained at 200R (2).

C. CdR concentration in blood and CdR content in urines of rats as functions of time after irradiation exposure to 200R of x-ray.

CdR concentration in the blood of unirradiated rats was found to be about 11 ug per ml. The concentration started to increase 3 to 6 hours and reached a maximum value of about 19 ug per ml 9 hours after irradiation. At about 18 hours after irradiation, the CdR concentration returned almost to the pre-irradiation level. Urinary CdR content started to increase 6 hours and reached a maximum value about 12 hours after the irradiation (2).

- D. Urinary excretion of CdR in man. Man excretes a much smaller quantity of CdR in urine than does a rat. An average pre-irradiation value was found to be about 0.007 mg of CdR per 24 hour urine as compared with 0.7 mg excreted by a rat in 24 hour urine. Approximately a two-fold increase from an average pre-irradiation value of 7 ug per 24 hour urine was observed in six of eight patients receiving 178 to 300 rads of local, partial or total body irradiation. Certain healthy individuals of Chinese ancestry consistently excreted at least 5 to 6 times as much CdR as other normal persons, e.g. subject II in Table I. It has been reported that approximately 25% of the persons of Chinese or Japanese ancestry consistently excrete abnormally large amounts of β -aminoisobutyric acid, which is an intermediate in thymine catabolism, and it has been shown that inability to further metabolize this amino acid is responsible for its greatly increased excretion by Orientals who have this characteristic as a genetically determined trait (3). Further studies are needed to determine whether the exceptionally high CdR excretion by a healthy person is also controlled by genetic factors. It is of interest to note, however, that subject IV, who is the mother of subject II, excreted the smallest amounts

of CdR among the subjects tested. The problem of whether this non-pathological abnormality found in a normal population involves any genetic factors remains to be studied (2).

- E. CdR deaminase activity in serum. The difference in radiosensitivity of CdR-uria in man and rat suggests that CdR is metabolized differently in these two species. A simple and sensitive technique was developed to assay CdR deaminase activity in serum which might be responsible for the difference in CdR metabolism between rat and man. It was found that the deaminase was completely absent in rat serum. In man, the deaminase activity ranged from 0.4 to 1.6 units per mg of serum protein (one unit of enzyme is defined as that amount of enzyme which can convert 1 μ mole of CdR to deoxyuridine in one hour). The preliminary results indicate that deaminase activity in serum is correlated to CdR content in urine, although more data are needed to draw any definite conclusion. We intend to assay deaminase and CdR content in large number of healthy individuals and patients with various diseases.
- F. Deaminase activity in an irradiated cancer patient. CdR deaminase activity in serum of a patient with malignant lymphoma was studied. The pre-irradiation deaminase activity was 1.6 units/mg protein. The activity dropped slightly 3 hours after the patient had received 300 rads of lower body irradiation. Nine hours after the irradiation, the activity was almost doubled and remained high 24 hours after the irradiation. Serum proteins were sharply increased 3 hours after the irradiation and returned to the pre-irradiation level 9 hours after the irradiation. The fact that the deaminase activity increases

despite the decrease in protein concentration indicates that the increase in deaminase activity is not due to the general increase in protein concentration.

- G. Other UV absorbing substances in human urines. According to our experimental results, it seems that CdR is not an end-product of pyrimidine metabolism in man. CdR released by irradiation may be further metabolized or reabsorbed in man. We have assayed the UV absorbing substances in pre- and post-irradiation urines by the use of an anion exchange column and pH gradient elution technique. Our preliminary results show that there are increases in uric acid and other purine derivatives after irradiation, but uracil, pseudo-uridine, and other pyrimidine derivatives seem not to be changed.

References:

1. Chen, I.W., Kereiakes, J.G., Friedman, B.I., and Saenger, E.L. Colorimetric analysis of deoxycytidine in urine after separation by ion-exchange column chromatography. Anal.Biochem. Vol. 23, 230-240, 1968.
2. Chen, I.W., Kereiakes, J.G., Friedman, B.I. and Saenger, E.L. Radiation-induced urinary excretion of deoxycytidine by rats and humans. Radiology, 91:343-348, 1968.

TABLE 1 DEOXYCYTIDINE CONTENT IN 24 HOUR URINES FROM SELECTED
HUMAN CONTROLS

<u>Deoxycytidine in 24 hour urine (μg)</u>								
<u>Subject</u>								Average \pm S.D
Age	Sex	Consecutive days of collection						
		1	2	3	4	5	6	
(I)	25 Male	9.7	8.1	7.3	7.1	9.4	8.2	8.3 \pm 1.1
(II)	33 Male	85.6	66.4	63.6	74.5	89.2	85.4	77.5 \pm 10.9
(III)	20 Male	11.5	9.4	8.0	7.3	-	-	9.0 \pm 2.0
(IV)	60 Female	3.2	2.4	3.0	-	-	-	2.9 \pm 0.4

II. Immunology

A. A major portion of our efforts has been expended thus far in learning to grow and purify the bacteriophages, T2 and :X 174. These are the two phages which are intended for use in the irradiated patients as antigens. Purification proved to be more difficult than originally anticipated.

1. Initially T2 phage was grown by inoculating an E. Coli B culture during the log growth phase. After the culture had cleared, indicating complete lysis of bacteria, it was centrifuged to remove bacterial cellular debris, dialyzed to remove media contaminants, and then passed through a 0.22 micron Millipore filter. However, this preparation proved to be extremely pyrogenic when injected intravenously into rabbits according to the method of the U.S. Pharmacopeia. Further purification steps of acid precipitation and ultracentrifugation yielded a preparation which had greatly reduced pyrogenicity in rabbits and was non-pyrogenic when injected intravenously into a monkey or intramuscularly into a human volunteer.
2. Bacteriophage :X 174 was grown by inoculating a log phase culture of E. coli C with the phage. After clearing of the culture, bacterial cellular debris and media contaminants were removed by centrifugation and dialysis respectively. The phage was then precipitated with ammonium sulfate and

resuspended in ammonium acetate. The preparation was then placed on a DEAE cellulose column and eluted in a step-wise fashion with ammonium acetate of increasing molarity. The phage was then concentrated by negative pressure dialysis and passed through a 0.22 micron Millipore filter. This final 4X 174 preparation again showed a greatly reduced pyrogenicity when injected intravenously into rabbits as did our final T2 phage.

- B. In assessing antibody responses to the phages we have decided to use the 50% neutralizing test rather than the determination of the K value as it is more accurate and more suitable for use with a large number of specimens. Sucrose density gradient ultracentrifugation of serum and the determination of antibody titer before and after treatment of the serum with 2-mercapto-ethanol will be used to distinguish the sequence of immunoglobulin response to the antigens. We are now in the process of immunizing normal individuals using these two bacteriophages.
- C. Dinitrochlorobenzene will also be administered to patients to assess the effect of total body irradiation on delayed type hypersensitivity.

III. Effects of Total and Partial Body Radiation on
Cognitive-Intellectual Functioning and Emotional Reaction:*⁺

Carolyn N. Winget, M.A.
Robert L. Kunkel, M.D.
Goldine C. Gleser, Ph.D.

The number of patients who have been evaluated by the psychiatric-psychological team now totals 20. In addition three patients who were given an initial psychological work-up and diagnostic interview were later dropped from the study. These three are excluded from this report as is one subject (069) who received sham radiation only. This report, therefore, is based on data provided by the 20 completed subjects. Descriptive data for this group are presented in Table 2. Clinical information on some patients discussed in this section will be found in previous reports (see Introduction).

A. Review of Procedures Used in Evaluation

Since the procedures for psychological evaluation of the subject have been changed somewhat from previous years, a brief outline of those research methods currently being used is given below.

1. After a patient is selected for partial or total

* The patients discussed in this section were described in DASA 1644 and an interium report for May 1, 1966 through April 30, 1967 and in this report.

+ Louis A. Gottschalk, M.D., Chairman of the Department of Psychiatry and Human Behavior, California College of Medicine serves as Consultant for this portion of the research.

Table 2
Biographic Data of 20 Radiation Patients Having Psychiatric Studies

Study No.	Sex	Race	Age	Marital Status	Type Ca.	Type Rad.	Survival Time (days)	Educa. ¹	Wechsler-Bellevue 10 ²		Halstead ³ Index	Initial Trails ⁴	
									Verb.	Perf.		A	B
057	F	N	57	W	Ovary	T 100	954 (A)	7	85	72	.79	-	-
*079	F	W	51	M	Breast	T 100	151 (A)	8	102	86	----	10	6
*075	F	W	60	Sep	Ovary	L 200	142 (A)	7	71	89	----	1	1
062	M	N	60	Sep	Colon	T 150	276	5	86	82	.75	1	1
066	M	N	63	W	Rectum	L 200	216	1	71	58	1.00	1	0
050	M	W	80	M	Rectum Bladder	U 200	204	5	107	117	.88	7	2
064	F	N	55	Sep	Sigmoid	L 300	186	8	70	66	.70	4	1
049	M	N	74	D	Rectum	L 200	177	10	116	--	1.00	-	-
067	F	N	52	W	Rectum	T 100	173	8	81	69	1.00	4	0
055	F	N	56	W	Rt.breast	U 200	156	2	70	79	.88	-	-
061	F	N	64	W	Metastatic	T 50	118	0	61	71	.67	-	-
065	F	N	64	W	Pancreas	L 200	93	6	115	100	.50	4	1
058	F	N	48	M	Cervix	T 50	89	8	86	84	.62	5	2
*070	M	N	62	D	Lung	T 150	77	0	80	89	.88	1	1
051	M	W	66	M	Lung	T 150	77	7	101	96	.88	8	3
*068	F	N	73	Sep	Endometrium	L 150	67	0	88	100	1.00	1	0

Table 2
(continued)

Study No.	Sex	Race	Age	Marital Status	Type Ca.	Type Rad°	Survival Time (days)	Educa.!	Wechler-Bellevue 10"		Halstead* Index	Initial Trails*	
									Verb.	Perf.		A	B
*078	M	N	55	M	Lung	T 200	61	10	91	101	----	6	2
056	M	N	53	Sep	Lung	U 100	43	0	79	80	.50	7	1
059	M	W	42	M	Kidney	T 150	41	8	105	82	.62	4	2
060	F	N	49	M	Rt. breast	T 150	34	3	92	82	.75	5	0
												8	8
												6	6
												5	5

* Processed or data analyzed since 6/67.
 (A) Alive 5/15/68
 ° These tests obtained before sham and irradiation.
 ! Education - years of elementary and high school.
 ° Type radiation - T = Total body
 U = Upper body
 L = Lower body

body radiation and has agreed to cooperate in the study, arrangements are made with the patient for a series of initial interviews. During this series a detailed but relatively unstructured interview is conducted and tape recorded. The following measures are also obtained:

- (a) Reitan Trails Test, parts A and B.
- (b) Catell's 16 PF IPAT, Form A.
- (c) Gottschalk-Gleser Values Inventory
- (d) Wechsler Depression Rating Scale
- (e) Clinical Depression Scale of Gottschalk.
- (f) Selected portions of the Wechsler-Bellevue Adult Intelligence Scale.
- (g) Clinical Hope and Denial Scales.
- (h) A structured questionnaire designed to pinpoint certain specific dynamics contributing to depression such as separation, guilt, shame, and masochism.
- (i) A five-minute tape recorded verbal sample.

2. Subsequently, the patient is seen and measurements are made on 10 additional occasions: pre- and post-sham, pre- and post-radiation treatment, and days 1, 3, 7, 14, 28, and 42. On each such occasion those measurements labeled a, d, e, and i are repeated.

Here and in subsequent portions of this report, the low survival group is defined as those who lived less than 100 days after treatment, while the high survival group is composed of those who lived longer than

100 days. Subjects tested since September of 1967 are not included in this analysis of IPAT data.

B. Biographical Data

As shown in Table 2, of the 20 subjects, 11 are female and 9 are male; 15 of the 20 are Negro; mean age is 60. With regard to marital status, 7 are married, 6 widowed, 5 separated, and 2 are divorced. These subjects range from 0 to 10 years of schooling with a mean of 5 years. On the Wechsler-Bellevue (WAIS) their range is from 63 to 116 with a mean I.Q. of 86.

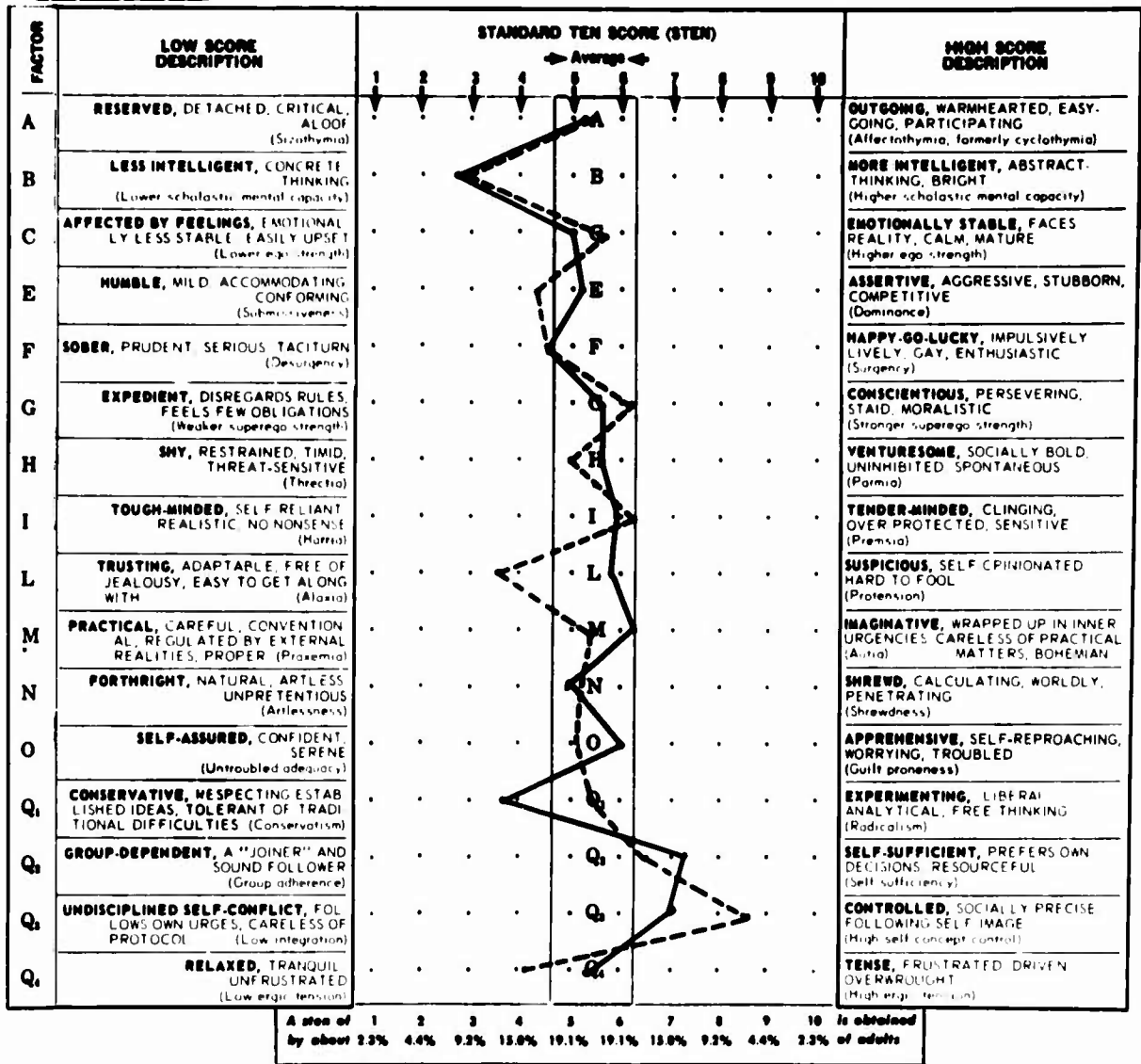
C. Personality Profile at Initial Interview

The Sixteen Personality Factor Questionnaire (Section III A,1,b) is administered at the time of the initial series of interviews. It is an objectively scored test which measures sixteen relatively independent psychological dimensions. Although it is designed to be self-administered by subjects whose educational level is equivalent to that of normal high school graduates, we have found that meaningful data can be secured by administering the test orally in an interview situation.

Figure 1 identifies the factors measured in this test and displays the profiles of the two survival groups. It should be noted in this connection that there was a tendency for the high survival group to show a higher mean age (64 years) than the low survival group (58 years). It is most reassuring to note the overwhelming similarity of this patient sample to Catell's general adult population norms based on large male and female samples (1). In 13 of the 16 factors (Figure 1) the group of radiation patients falls well within the average range for a normal adult general population. The deviation of both low and high survival group on Factor B (i.e. both



16 P F TEST PROFILE



----- High Survival Group, N = 7

———— Low Survival Group, N = 5

Figure 1 IPAT Profiles for Low and High Survival Groups.

are less intelligent, more concrete in thought processes and display less scholastic mental capacity) substantiates the information provided by the Wechsler-Bellevue (WAIS), as well as our own subjective knowledge of the patient population usually served by a large urban general hospital.

Another finding from the data provided by the 16 PF is that the high survival group is significantly lower in Factor L than is the low survival group or the norms provided by a general adult population. Thus, even before treatment has begun, those we have designated post hoc as long survivors are more trusting, adaptable, free of jealousy and easy to get on with, while those who are low survivors more nearly resemble the general population on this dimension.

On Factor Q_1 , the low survival group was found to be more conservative, more respecting of established ideas, and more tolerant of traditional difficulties, while the high survival group resembled the normal population norms in this respect.

Both low and high groups showed a tendency to be somewhat more self-sufficient, preferring their own decisions, and more resourceful than indicated by the averages for the general population.

Both low and high survival groups tended to be made up of persons who were somewhat more controlled, more socially precise, more self-disciplined and compulsive than general population norms as measured by Factor Q_3 . However, the high survival group was significantly higher ($p < .01$) than the low survival group on this score.

Depression Rating Scales

Mean subgroup scores for the Wechsler Depression Rating Scale (DRS) are given in Figure 2 for all 20 subjects. Part A refers to scores on

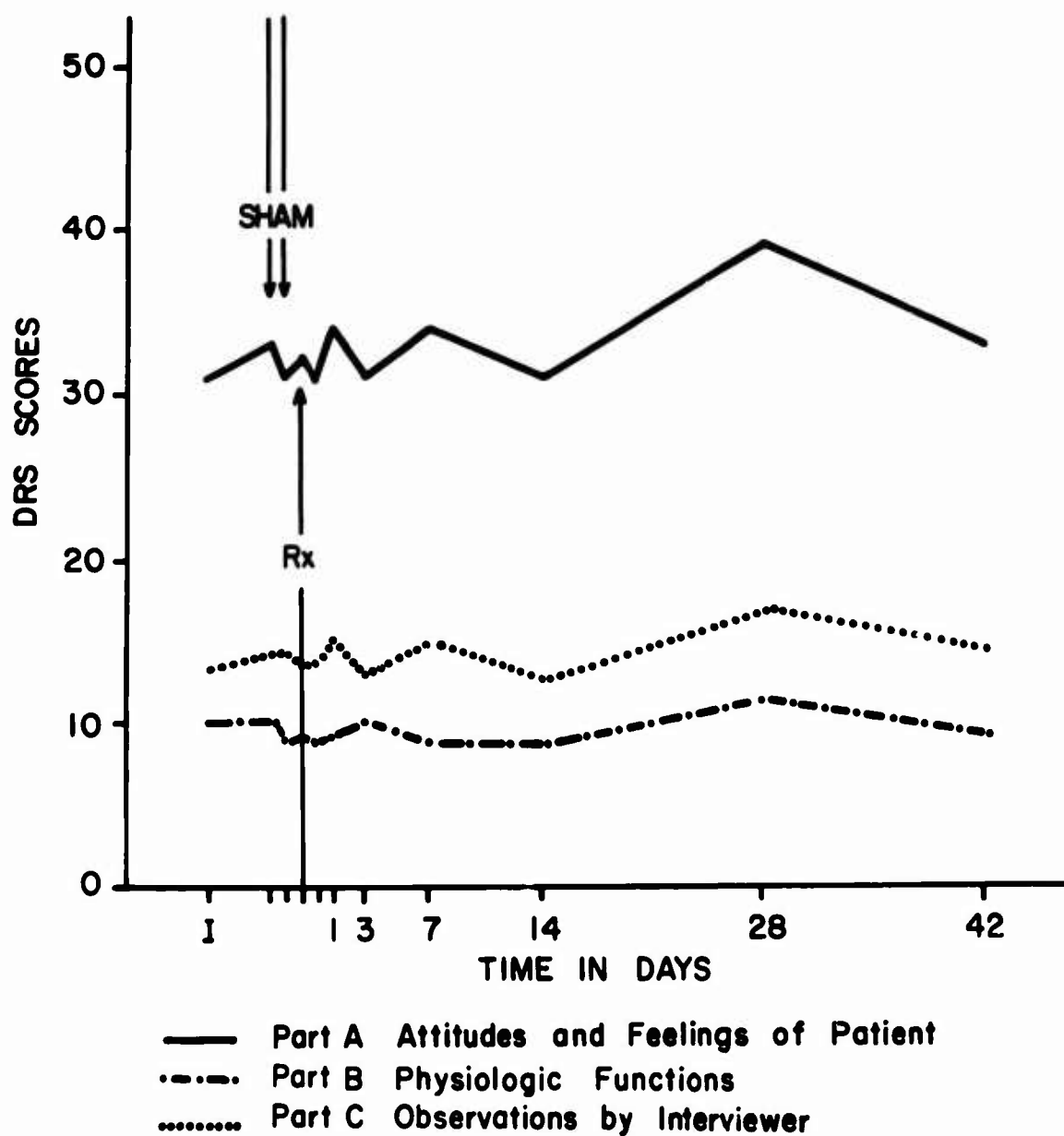


Figure 2 Mean Wechsler Depression Rating Scale Scores.

the section of the scale relating to the attitudes and feelings of the patient; part B presents scores obtained on items referring to physiologic functions; and part C gives scale scores based on observations made by the interviewer. As noted in previous annual reports for this project, all subjects tend to show at least mild depression throughout the period of study. After day 7, the sub-scales tend to show highly similar trends.

Figure 3 shows the mean DRS scores for the total overall ratings for the entire group of 20 patients as well as for patients divided into groups on the basis of low and high survival time. It should be noted with regard to our use of a "high" survival group that three subjects included in the group are still alive. In subsequent data analysis, therefore, their rank relative to others in the high survival group will shift, thus making for ultimate change in results as presently reported.

Scores obtained from the Clinical Depression Scale devised by Gottschalk are presented graphically in Figure 4. As might be expected, there is a great deal of overall similarity in the trends shown by these two types of measures of depression.

The mean DRS scores as shown in Figure 3 indicate moderately high average depression ratings at day 7 followed by a marked dip at day 14 and a sharp increase for day 28. These data on depression ratings are difficult to interpret for a number of reasons. There is unavoidable attrition leading to unequal numbers of measures for different experimental days, i.e. the number of scores contributing to the mean differs from one day to another. In addition, the already difficult problems of handling sequential data are made more difficult by the unequal time periods sampled in this particular design. Two subjects (049 and 050)

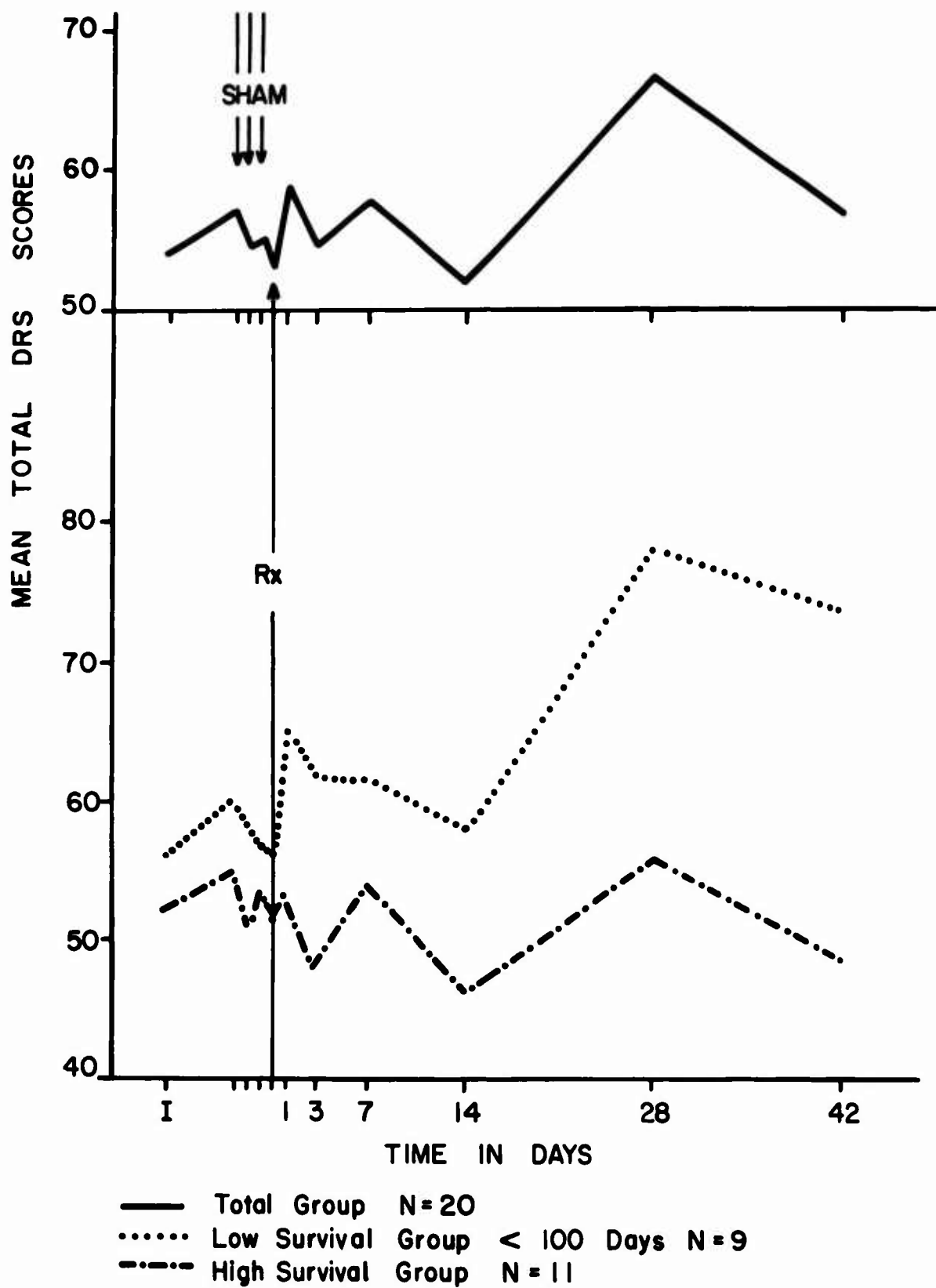


Figure 3 Total Depression Ratings (See Table 2).

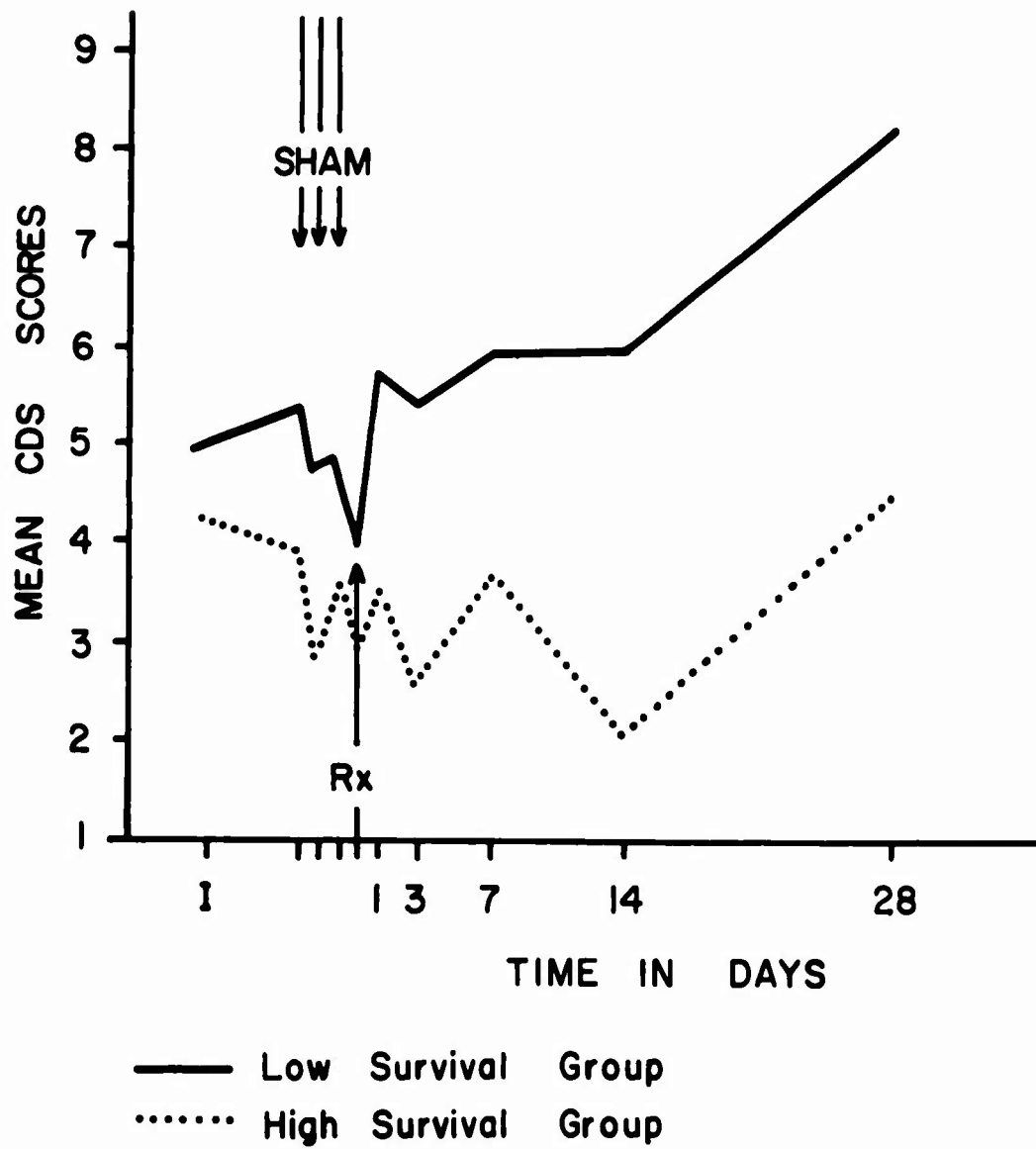


Figure 4 Clinical Depression Scores (Scale of Gottschalk).

were therefore eliminated from the high survival group because of unusually large gaps in their data and focused on five time periods: initial, pre-treatment, 7 day, 14 day, and 28 day. With these modifications, the overall level of depression is significantly different, i.e. the low survival group tends to be more depressed throughout the period that we have studied than those who survive longer than 100 days. However, in addition to this, the low survival group tends to show a sharp increase in depression from the 14th to the 28th day. This increase is significantly greater than that obtained by the high survival group for the few subjects that we have studied so far.

Despite these differences in DRS scores, there are considerable similarities in the variations in depression over the first month of study of each subject. Depression tends to increase slightly to the 7th day after treatment and then shows a sharp decrease for both groups in the 14th day post-treatment measurement. Just what this might mean in terms of radiation effects is not clear at this time, but it is something which certainly should be closely watched as subsequent subjects are studied.

Hope Rating Scale

The Clinical Hope Scale is a 1 to 15 point scale, filled out by the member of the team conducting the initial diagnostic interview. It rates the degree of hope that the patient has with respect to a favorable and optimistic attitude regardless of the patient's realization of the possibility of a fatal outcome of his disease. As shown in Table 3, the Clinical Hope Scale correlates positively with length of survival for the 20 subjects studied to date.

TABLE 3
Initial Verbal Sample Rank Order Correlations (N = 20)

	(1) <u>Hope</u>	(2) <u>HS</u>	(3) <u>HR</u>	(4) <u>CI</u>	(5) <u>DRS</u>	(6) <u>CDS</u>	(7) <u>Days Survival</u>	<u>Clinical Hope</u>
(1) Hope	-	0	.43	-.08	.09	-.13	.44	.03
(2) Health-Sickness		-	.21	-.16	.18	-.01	.36	.40
(3) Human Relations			-	-.38	.18	-.07	.04	.03
(4) Cognitive Impairment				-	-.17	-.02	-.23	-.26
(5) Depression Rating Scale (Total)					-	.83	-.19	-.58
(6) Clinical Depression Scale						-	-.33	-.65
(7) Days Survival							-	.46

Measures Based on Verbal Behavior

Affect Scales. A number of rating scales devised by Gottschalk and Gleser have been applied to the subject's verbal samples collected at each of the 11 measurement times. Mean scores for four affects as measured by content analysis of the verbal material (anxiety, hostility directed outward, hostility directed inward, and ambivalently directed hostility) were analyzed. There is no important difference in these scores by survival groups, i.e. the means for the high and low survival groups for these four measures of affect do not differ significantly. As shown in Figure 5, there is a tendency for anxiety to dip sharply at the sham treatment period and to increase just prior to treatment time and then to decrease and level off. Hostility directed outward tends to increase at the time of post-sham measurement and dip and remain quite stable. There is no evidence that radiation has any appreciable effect on any of these affects as measured by the verbal sample method.

Human Relations, Hope, Health-Sickness Scales. Table 3 also gives the rank order correlations of four verbal behavior measures with the two depression measures and the days of survival. All of these measures are based on scores obtained at the time of the initial series of interviews. The verbal behavior measure of Hope correlates positively with Human Relations and with days of survival. There appears to be no correlation between Hope as measured in the verbal behavior and references to Health-Sickness. It is interesting to note that although the Clinical Hope Scale shows essentially no correlation with Hope as measured by content analysis of the verbal behavior, both show a high positive correlation with survival time.

Cognitive Impairment. In view of the difficulty in obtaining valid and reliable measures of cognitive impairment, we have increasingly focused our attention on the development and improvement of a scale designed to measure this dimension through the content analysis of verbal behavior. Utilizing the verbal behavior of other diagnostic groups we are continuing our attempts to improve the usefulness of a Cognitive Impairment Scale which was originally derived from selected items making up our Scale of Personal Disorganization and Social Alienation (Schizophrenic Scale).

The analysis of the Cognitive Impairment scores presented in this report is based on the currently used weighting system for this scale as reported in Gottschalk and Gleser (2). On this basis, we find that there is a negative correlation between the Cognitive Impairment scores for 20 radiation patients and their scores on the Wechsler Adult Intelligence Scale ($r = -.39$ total WAIS and Cognitive Impairment), i.e. the greater the impairment the lower the I.Q. for these subjects. This tends to substantiate the validity of the scale.

We have investigated the Cognitive Impairment scores of subjects by type of radiation received, i.e. total, lower, and upper, and do not find any significant differences among these three groups. Moreover, those designated as high or low survival on the basis of days of survival after treatment were randomly distributed among these three groups.

The mean Cognitive Impairment scores for the low survival and high survival groups are presented graphically in Figure 6. The low and high groups start with almost identical scores as measured by the Cognitive Impairment scale. They remain highly similar at the time of the pre-sham

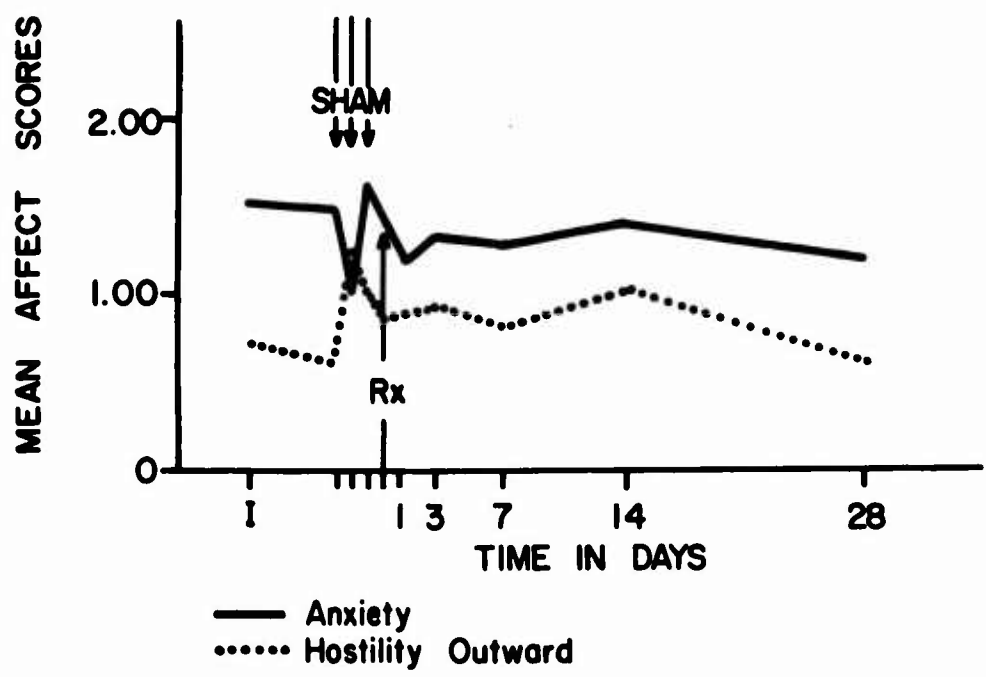


Figure 5 Average Affect Scores from Verbal Behavior.

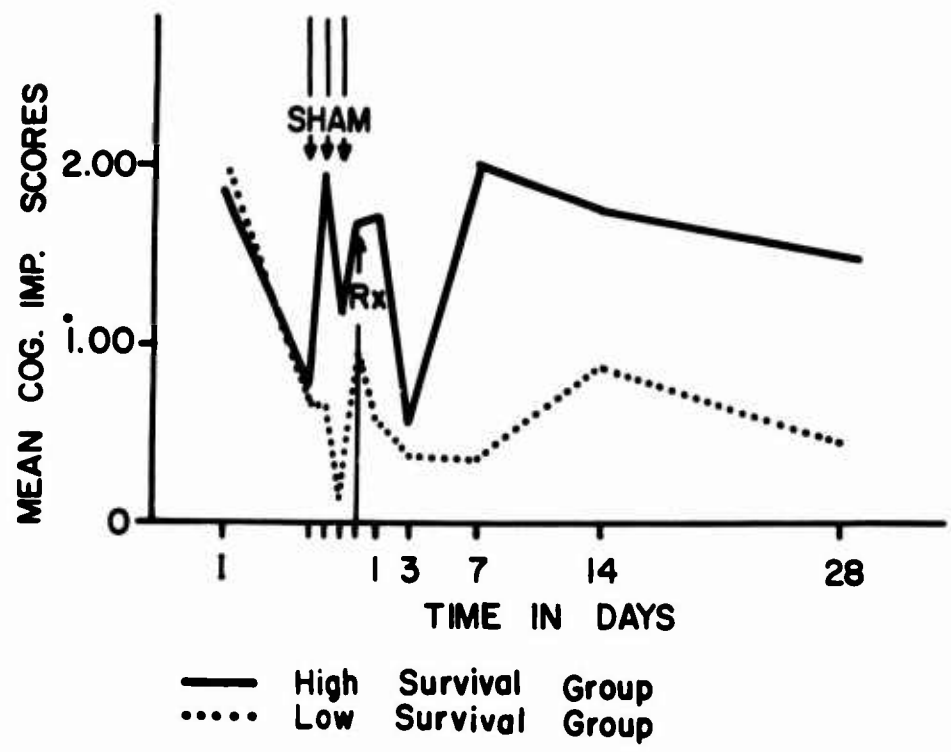


Figure 6 Average Cognitive Impairment Scores in Low and High Survival Groups.

measurement. However, at the post-sham occasion the group who will later show a high survival rate deviates radically in the direction of greater cognitive impairment. Both low and high survival groups show a dip in average cognitive impairment scores at the time of their pre-treatment measures and an increase subsequently at the post-treatment period. There is a marked rise in cognitive impairment scores of the high survival group at day 7, and subsequent mean scores remain consistently higher than do those of the low survival group. At day 7 there is a rank order correlation of $r = .52$ between cognitive impairment scores and days of survival for the entire group.

There is not enough data to interpret this important finding at this time. The most tempting hypothesis is that radiation does have some effect on functioning in this area. However, the divergence of the two groups prior to actual radiation gives rise to the speculation that already at this time there are factors operating which may differentially affect cognitive processes and physiological outcome for these two groups. The material derived from the initial IPAT lends confirmation to such a speculative hypothesis. Thus one might ask whether the high survivals as a group "believe" more in the possible palliative aspects of partial or total body radiation and therefore at some level react with greater cognitive impairment and lowered levels of depression. Alternatively, it is possible that feelings regarding their imminent death in the low survival group are so strong that they over-ride or mask any cognitive deficit, perhaps via the mechanism of increased vigilance. It is not clear at this time to what extent some of this variation in scores may be due to the effects of radiation per se.

References :

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2. Gottschalk, L.A. and Gleser, G.C. The measurement of Psychological States Through the Content Analysis of Verbal Behavior. (University of California Press, 1969).
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IV. Clinical Studies:

Patients who were irradiated responded with the same incidence of symptoms and signs of the prodromal and manifest disease stage of the radiation syndrome as noted previously. The two patients treated with 200 rad total body irradiation were infused intravenously with autologous bone marrow cells. Radiation doses for these patients are given in Table 4.

Data on autologous marrow infusions in five patients is given in Table 5.

The first of the patients (077) was treated with 0.79×10^9 marrow cells on the second day after irradiation. These cells had been stored at -80°C for nine days. Trypan blue viability testing revealed 48% viable cells. There was no apparent response to this replacement.

Subsequently it was thought advisable to discontinue storage in a glycerol solution at -80°C and to hold the marrow cells at -4°C in a standard refrigerator without glycerol, for twenty-four hours. Viability of cells with such a technique is thought to be 95-100%.

Patient 078 had 4.16×10^9 marrow cells (after WBC correction) removed on the day prior to radiation, stored at -4°C and infused intravenously on the day of radiation. Trypan blue exclusion studies revealed 96% viable cells. This number represented 0.8×10^8 cells per Kg. which is close to the minimum of 1×10^8 cells per Kg. as recommended by van Bekkum (D.W. van Bekkum and M.J. deVries, Radiation Chimeras, p/200, Academic Press). There seemed to be a delay in the fall in WBC of this

patient, and the lowest platelet count was 125,000/mm³. Statistical analysis of the platelet data suggests the possibility of a marrow "take".

In the apparently successful marrow graft in the Pittsburgh accelerator accident of October 1967, the patient received 9×10^9 nucleated cells directly from an identical twin. If, as is thought from our data, there is a suggestion of a "marrow take" at 4.16×10^9 cells (case 078) and no takes using frozen marrow, one then may suspect that a lower level of cells for successful marrow take might be about 4×10^9 cells. Further studies of this aspect of therapy are indicated.

TABLE 4

Radiation Dosimetry

Patient No.	Midline Air Exposure Roentgens	Midline Tissue Dose rad
072	500	300 Lower
075	290	200 Lower
077	290	200 TBR
078	302	200 TBR
079	139	100 TBR
081	139	100 TBR
082	435	300 Lower

Table 5
Patients Receiving Autologous Marrow Infusion

Study No.	Weight (kg)	Total Body Dose (rad)	Date of Rx	Date of Infusion	Total Marrow Cells day of Collection	% Viability @ time of Collection	Total Marrow Cells day of Infusion	% Viability @ time of Infusion	Volume Infused Bone Marrow ml	Solution ml	Total
078	52.0	200	12/5/67	12/5/67	4.16×10^9	100	4.16×10^9	96	Unfrozen 330	TC 199 99	429
077	49.1	200	11/7/67	11/9/67	2.0×10^9	99	$.79 \times 10^9$	48	Frozen 323	TC 199 502	825
070	74.1	150	3/2/67	3/13/67	$.36 \times 10^9$	95	$.33 \times 10^9$	68	Frozen Marrow + *O.G. Media 320	33 1/3% Dextrose 160	480
053	55.4	200	5/8/65	5/27/65	1.5×10^9	99	1.4×10^9	57	Frozen Marrow + O.G. Media 400	33 1/3% Dextrose 200	600
051	43.2	150	5/1/65	5/25/65	2.3×10^9	100	1.6×10^9	55	Frozen Marrow + O.G. Media 370	33 1/3% Dextrose 200	550

* Osgood-Glycerol media

V. Result of Discriminant Function Analysis to Distinguish Between Groups Given Low and High Radiation Doses

A. Initial Studies to Determine a Baseline:

In order to develop an equation to attempt prediction of low and high dose radiation, an initial group of 44 patients was studied. They were divided into two subgroups: those patients receiving partial body irradiation or total body irradiation of less than 125 rads comprised group one; patients receiving total body irradiation of at least 125 rads comprised group two.

The statistical technique of discriminant function analysis was used to study the extent to which the different subgroups overlapped one another or diverged from one another. The hypothesis underlying the use of this technique is that a set of measurements on each patient may be used as an indicator of the particular type of irradiation which a person has undergone. The discriminant analysis helps one to learn what measurements are most effective in distinguishing between the groups, how best to combine the measurements, and how successfully the distinction can be made.

In selection No. 1, the measurements used are:

X_1 = day post Rx on which minimum RBC is obtained

$X_2 = \frac{\text{RBC post Rx reading on minimum day}}{\text{RBC pre Rx mean}}$

$X_3 = \text{RBC slope} = \frac{X_2 - 1}{X_1}$

X_4 = day post Rx on which minimum WBC is obtained

$$X_5 = \frac{\text{WBC post Rx reading on minimum day} \times 10^{-1}}{\text{WBC pre Rx mean}}$$

$$X_6 = \text{WBC slope} = \frac{X_5 - 1}{X_4}$$

X_7 = day post Rx on which minimum platelet count is obtained

$$X_8 = \frac{\text{platelet post Rx reading on minimum day}}{\text{platelet pre Rx mean}}$$

$$X_9 = \text{platelet slope} = \frac{X_8 - 1}{X_7}$$

The discriminant function obtained is:

$$Z = -.00024 X_1 + .04433 X_2 - .01482 X_3 + .00320 X_4 + .07492 X_5 + .20777 X_6 + .00247 X_7 + .18293 X_8 - .48557 X_9.$$

The values of the discriminant function are listed on IBM printout in rank order, showing the two groups separately. The discriminant function value of .26977 is the point which best* separates the two given groups. A patient whose function value is greater than .26977 falls in group 1; one whose function value is less than .26977 falls in group 2. There are 5 patients which are wrongly classified in this initial group. One of these patients (013) received three divided doses of 50 rad each in 17 days.

* "best" means the number of patients misclassified is minimized.

B. Studies of 10 New Patients:

When measurements on 10 new patients were used and the values of the above discriminant function obtained the results were as follows:

<u>Patient No.</u>	<u>Dose (rad)</u>	<u>Group</u>	<u>Z value</u>	<u>Classification according to Z valu</u>
061	50	I	.35522	I (correct)
062	150	II	.22809	II (correct)
063	300	I	.31263	I (correct)
064	300	I	.33402	I (correct)
065	200	I	.26118	II (incorrect)
066	200	I	.27663	I (correct)
067	100	I	.33085	I (correct)
068	150	I	.31820	I (correct)
070	150	II	.30207	I (incorrect)
072	300	I	.48115	I (correct)

The number of patients wrongly classified is 2 out of 10.

Looking at Selection No. 3, one sees that when only measurements relating to WBC and Platelets are used, the discriminant function wrongly classifies only 4 out of 44 patients. It seems that the elimination of RBC has made the 2 groups more distinguishable. The discriminant function is as follows:

$$Z = .00325 X_4 + .08427 X_5 + .20821 X_6 + .00231 X_7 + .18228 X_8 - .47907 X_9.$$

The discriminating value is .23900, i.e. a patient whose Z value is greater than .23900 is classified as coming from group 1; a patient whose Z value is less than .23900 is classified as coming from group 2.

The test of this function again using the 10 new patients gave the following results:

<u>Patient No.</u>	<u>Dose (rad)</u>	<u>Group</u>	<u>Z value</u>	<u>Classification according to Z value</u>
061	50	I	.33494	I (correct)
062	150	II	.19870	II (correct)

<u>Patient No.</u>	<u>Dose (rad)</u>	<u>Group</u>	<u>Z value</u>	<u>Classification according to Z value</u>
063	300	I	.28210	I (correct)
064	300	I	.33208	I (correct)
065	200	I	.23945	I (correct)
066	200	I	.24457	I (correct)
067	100	I	.31328	I (correct)
068	150	I	.28500	I (correct)
070	150	II	.27294	I (incorrect)
072	300	I	.44544	I (correct)

The number of patients wrongly classified is 1 out of 10.

When measurements relating to WBC (X_4 , X_5 , X_6) were used to obtain a discriminant function, the groups were shown to overlap, indicating that these WBC measurements are not sufficient to distinguish the two groups.

The measurements relating to Platelet count only, however, seemed to provide better discriminating power. (See Selection No. 2). The discriminant function is:

$$Z = .00272 X_7 + .17572 X_8 - .27057 X_9.$$

The discriminant function value of .11365 is the point which best separates the two groups. A patient whose function value is greater than .11365 falls in group 1; one whose function value is less than .11365 falls in group 2. There are 5 patients which are wrongly classified.

When Platelet measurements on the 10 new patients were used and values of the above discriminant function obtained, the results were as follows:

<u>Patient No.</u>	<u>Dose (rad)</u>	<u>Group</u>	<u>Z value</u>	<u>Classification according to Z value</u>
061	50	I	.18525	I (correct)
062	150	II	.10199	II (correct)
063	300	I	.19308	I (correct)
064	300	I	.19300	I (correct)
065	200	I	.13987	I (correct)
066	200	I	.15218	I (correct)

<u>Patient No.</u>	<u>Dose (rad)</u>	<u>Group</u>	<u>Z value</u>	<u>Classification according to Z value</u>
067	100	I	.30956	I (correct)
068	150	I	.23313	I (correct)
070	150	II	.15480	I (incorrect)
072	300	I	.44937	I (correct)

One patient out of 10 is wrongly classified.

Given the existence of two populations and a sample of patients from each, the problem of setting up a rule, based on certain measurements from these individuals which will enable one to allot a new individual to the correct population when we do not know from which of the two he comes, was handled by methods of discriminant function analysis. A group of 44 patients divided into two groups of 28 and 16 was used as samples of the two populations. A series of nine measurements was made on each patient: three relating to RBC, three relating to WBC, and three to Platelet count. It was shown by discriminant analysis that RBC measurements contributed nothing to the discriminating power of the nine variables; also that the three variables relating to Platelet count were as accurate in correctly classifying ten new individuals into the two populations as the six variables together relating to WBC and Platelet count. WBC variables alone were not accurate discriminators.

The following are the results obtained when the previously calculated discriminant functions were used on 6 patients of this report in order to predict their group.

Using all 9 variables and the discriminant function

$$Z = .00024 X_1 + .04433 X_2 - .01482 X_3 + .00320 X_4 + .07492 X_5 + .20777 X_6 + .00247 X_7 + .189293 X_8 - .48557 X_9, \text{ we obtained these results:}$$

<u>Patient No.</u>	<u>Dose (rad)</u>	<u>Group</u>	<u>Z value</u>	<u>Classification according to Z value</u>
075	200	I	.32335	I (correct)
077	200	II	.17414	II (correct)
078	200	II	.24032	II (correct)
079	100	I	.33742	I (correct)
081	100	I	.35686	I (correct)
082	300	I	.87409	I (correct)

Using variables 4 through 9 and the discriminant function

$$Z = .00325 X_4 + .08427 X_5 + .20821 X_6 + .00231 X_7 + .18228 X_8 - .47907 X_9,$$

the results were:

<u>Patient No.</u>	<u>Dose (rad)</u>	<u>Group</u>	<u>Z value</u>	<u>Classification according to Z value</u>
075	200	I	.29308	I (correct)
077	200	II	.15118	II (correct)
078	200	II	.21885	II (correct)
079	100	I	.32634	I (correct)
081	100	I	.32528	I (correct)
082	300	I	.90199	I (correct)

Using variables 7 through 9 and the discriminant function

$$Z = .00272 X_7 + .17572 X_8 - .27057 X_9, \text{ we obtained:}$$

<u>Patient No.</u>	<u>Dose (rad)</u>	<u>Group</u>	<u>Z value</u>	<u>Classification according to Z value</u>
075	200	I	.11574	I (correct)
077	200	II	.08077	II (correct)
078	200	II	.125069	I (incorrect)
079	100	I	.12679	I (correct)
081	100	I	.21323	I (correct)
082	300	I	.20117	I (correct)

Patient 078 had received an autologous infusion of 4.9×10^9 nucleated marrow cells on the day of radiation which may have affected his hematological response.

VI. Case Histories:

Study No. 072

Patient: L.R.

Chart No. CGH 461-003

This patient, a 62 year old Caucasian female, was admitted to St. Mary's Hospital, Cincinnati, Ohio on June 13, 1967, for thrombophlebitis and abdominal discomfort. Gastrointestinal x-rays revealed a retroperitoneal mass displacing the stomach upward and anteriorly. IVP revealed a non-functioning right kidney. A right perirenal biopsy of the mass was performed on July 6, 1967 and read as malignant lymphoma (S1123-67).

On July 27, 1967, approximately 195 c.c. of bone marrow was aspirated and stored. The patient was given sham radiation on August 2, and August 3, 1967, with no adverse side effects.

She was treated on August 4, 1967, with 300 rad midline tissue dose (500 R midline air exposure) of partial body radiation to the lower body. Immediately following therapy she became nauseated and vomited several times that day.

The remainder of her hospital stay was uneventful, and she was discharged August 25, 1967, 21 days post PBR.

She was readmitted August 26, 1967, with left lower lobe pneumonia. After a successful course of antibiotic therapy, she was discharged to her home on September 27, 1967, 54 days post PBR.

Study No. 072

(page 2 continued)

The patient continued in satisfactory condition until April 21, 1968, when she was admitted to Cincinnati General Hospital for thrombophlebitis of her right leg. She was placed on anticoagulant therapy and discharged to her home on May 8, 1968, 278 days post PBR.

Study No. 075

Patient: N.C.

Chart No. CGH 409-278

This patient, a 60 year old white female with known granulosa cell cancer of the right ovary, diagnosed October 1, 1962, (SP 62-2623) by laparotomy, hysterectomy and bilateral salpingo-oophorectomy, was admitted to Cincinnati General Hospital October 16, 1967, for evaluation of a lung nodule seen on a chest film taken October 16, 1967 and consideration of partial body irradiation for control of her metastatic disease.

On October 24, 1967, bone marrow aspiration from the posterior iliac revealed only a few cells in clotted specimens. No bone marrow was stored.

She was shammed October 30, 1967, with no adverse side effects.

The patient was treated with 200 rad midline tissue dose (290 R midline air exposure) of partial body irradiation to the lower body on October 31, 1967. She experienced nausea and vomiting immediately after treatment but otherwise tolerated it well.

She was discharged November 3, 1967, to her home and will be followed in Tumor Clinic.

On December 13, 1967, 43 days post PBR, she continues to do well and her hemogram remains stable.

The patient was seen March 21, 1968, 142 days post PBR, in Tumor Clinic because of severe back pain which radiated down the right leg. She received 1450 R of Cobalt 60 teletherapy from March 22, 1968 to

Study No. 075

(page 2 continued)

April 5, 1968, at which time it was discontinued due to her inability to tolerate additional treatments.

Patient received 2000 R Cobalt 60 teletherapy from May 21, 1968 to June 7, 1968 to the right side of pelvis for relief of pain and possible improvement in quadriceps function.

At completion of therapy, there was some return of function of the quadriceps muscle and minimal pain relief.

Patient was again admitted to Cincinnati General Hospital on June 14, 1968 due to severe right hip and leg pain.

Chest x-ray on July 9, 1968 revealed two lesions, one in left hemithorax was markedly increased since March 21, 1968, and one in right hemithorax was not present on March 21, 1968. There was widening of the mediastinum.

A percutaneous chordotomy was performed on June 24, 1968 with no relief of pain. The chordotomy was repeated on July 23, 1968, with minimal relief of pain in right hip.

The patient was discharged to her home on July 29, 1968.

Due to persistent pain she was admitted to Drake Memorial Hospital, Cincinnati, Ohio, on August 27, 1968, 335 days post PBR.

Study No. 077

Patient: G.S.

Chart No. H.H. 672-144

This 63 year old Caucasian male was seen initially in January, 1967 because of progressive hoarseness. No improvement was noted with local therapy. In February, 1967, because of difficulty in breathing, a direct laryngoscopy and biopsy (SP 67-5913) revealed a fungating tumor involving the left lateral pharyngeal wall and pyriform sinus. A tracheostomy was also performed due to a partial obstruction of the airway. The patient was treated with pre-operative Cobalt 60 teletherapy receiving 4000 R minimal tumor dose over a period 31 days, from March 2, 1967, to April 4, 1967. Following this course of therapy, there was regression of the tumor mass. Subsequently, a radical left neck dissection was performed. The patient then received 3000 R to the left lateral neck over a period of 21 days, from May 10, 1967, to June 1, 1967.

This patient was admitted to Holmes Hospital on October 30, 1967, for total body irradiation. On October 31, 1967, 300 ml of bone marrow was aspirated with ease from both posterior iliac crests.

He was shamed on November 6, 1967 and treated on November 7, 1967 with 200 rad midline tissue dose (290 R midline air exposure) of total body irradiation. He experienced only slight nausea and vomited once following treatment.

On November 9, 1967, $.79 \times 10^9$ of filtered bone marrow cells were infused. Viability by Trypan Blue was 48% on day of infusion. He tolerated the procedure well with no change in temperature, pulse,

Study No. 077

(page 2 continued)

respiration, or blood pressure. Hemoglobinuria was noted immediately following infusion; however, this cleared by morning.

The patient was discharged to his home on November 10, 1967. His hemogram remained stable until November 27, 1967. On December 1, 1967 his white count reached a low of 400 with 18,000 platelets. His condition continued a downhill course, and on December 9, 1967, he expired, 31 days post TBR.

Study No. 078

Patient: L.H.

Chart No. CGH 464-517

This patient, a 55 year old Negro male, was admitted to Cincinnati General Hospital on November 27, 1967, with metastatic bronchogenic carcinoma. This was his first admission to CGH, and pathology reports from out of town were unobtainable.

He had previously received local irradiation to the primary and to local nodes in the neck and axilla. In the previous month, progression of his disease was noted. A liver scan on November 30, 1967 revealed enlargement. Chest x-rays on November 27, 1967, revealed probable carcinoma of the right lung. On December 4, 1967, an upper gastrointestinal series revealed displacement and invasion of the upper one-half of the stomach by several masses.

The patient was shamed on December 1, 1967, with no adverse side effects. Approximately 330 ml of bone marrow was aspirated from the posterior iliac rests on December 4, 1967.

On December 5, 1967, the patient was treated with 200 rad midline tissue dose (302 R midline air exposure) of total body irradiation. He tolerated the procedure well.

Following treatment on December 5, 1967, 4.16×10^9 autologous marrow cells were infused with no adverse side effects or hemoglobinuria noted. He was discharged to his home on December 8, 1967.

His hemogram remained stable until January 2, 1968, when his white count dropped to 900. Due to steady deterioration and increased pain he was admitted to the Veterans Administration Hospital, where he expired February 4, 1968, 61 days post TBR.

Study No. 079

Patient: N.W.

Chart No. CGH 464-015

This patient, a 50 year old Caucasian female, was admitted to Cincinnati General Hospital on December 8, 1967, for total body irradiation.

On May 6, 1964, a left radical mastectomy was performed at Christ Hospital, Cincinnati, Ohio. The biopsy report (SP 64-2706F) revealed infiltrating duct cell carcinoma with metastases. A bilateral oophorectomy was performed in January, 1967, because of bony metastases. She had been on chemotherapeutic drugs from April, 1967, to August, 1967; however these were discontinued because of progression of bony metastases and the appearance of skin nodules.

A skin biopsy on December 8, 1967, (SP 67-4063) revealed metastatic carcinoma of the skin. On December 11, 1967, bone marrow aspiration from the sternum and right posterior iliac crest revealed a few marrow elements. No marrow was stored.

She was shammed on December 11, 1967, with no adverse side effects. The patient was treated with 100 rad midline tissue dose (139 R midline air exposure) of total body irradiation on December 12, 1967. She experienced nausea for approximately 24 hours following treatment but otherwise tolerated it well.

She was discharged on December 21, 1967, to her home to be followed by her physician.

She continued in satisfactory health until January 10, 1968, when her hemoglobin and hematocrit began to drop and reached a low of 4 gm of

Study No. 079

(page 2 continued)

hemoglobin and 12% hematocrit on January 25, 1968. On January 26, 1968, she was admitted to Epp Memorial Hospital, Cincinnati, Ohio, where she received 4 units of whole blood and was discharged on January 31, 1968. At that time prednisone 15 mgm P.O. Q6h was started.

On February 13, 1968, 61 days post TBR, her condition was improved. Her hemoglobin was elevated to 9.6 gm and her hematocrit was 31%.

The patient continued to have a satisfactory clinical course until April 25, 1968, when she was admitted to Epp Memorial Hospital because of a nasal hemorrhage. Her hemoglobin fell to 7.6 gm and her hematocrit to 24%. She received 2 units of packed red cells and was discharged to her home on May 4, 1968, 144 days post TBR.

Study No. 081

Patient: I.S.

Chart No. CGH 409-670

This patient, a 52 year old Caucasian female, was admitted to Cincinnati General Hospital on September 15, 1967, because of a mass in the right mediastinum.

Bronchoscopy and biopsy (SP 673171) on September 18, 1967 revealed poorly differentiated carcinoma consistent with bronchogenic origin. Superior vena-cavagram on September 18, 1967 revealed complete venous obstruction. A chest film on September 22, 1967 showed a right upper lobe mass. She was treated with Cobalt 60 teletherapy 3500 R total tumor dose to the mediastinum from September 18, 1967 to October 3, 1967. Liver scans on October 6 and 11, 1967 revealed two defects in an enlarged liver consistent with multiple foci of metastatic disease. She received 1500 R minimal tumor dose from October 25, 1967 to November 3, 1967 to the left scapula to relieve pain.

This patient was last admitted on January 2, 1968 with a history of progressive enlargement of venous structures of the upper extremities and neck, weight loss, anorexia, malaise, and shortness of breath.

On January 15, 1968, a left posterior iliac bone marrow was obtained with ease. The patient was also shammed on this date with no adverse side effects.

She was treated on January 16, 1968, with 100 rad midline tissue dose (139 R midline air exposure) of total body irradiation. She tolerated the procedure well.

Study No. 081

(page 2 continued)

Due to progressive pain in the left hip, she was treated with 1500 R air dose in three treatments of 500 R each from January 23, 1968 to January 26, 1968.

On February 1, 1968, a course of 2000 R to the upper mediastinum was planned; however, after 800 R tumor dose, the patient's condition became so clinically poor that further treatment was suspended.

She expired on February 9, 1968, 24 days post TBR.

Study No. 082

Patient: L.R.

Chart No. CGH 465-713

This patient, a 49 year old Negro female, was admitted to Cincinnati General Hospital on January 18, 1968, with abdominal pain, hematuria, and shortness of breath of two weeks duration.

She was admitted to University Hospitals of Cleveland June 15, 1963, with abdominal pain, weight loss, and anorexia. After x-rays suggested a neoplastic lesion in the transverse colon, an exploratory laparotomy was performed. An inflammatory mass with an abscess formation and carcinoma of the first one-third of the transverse colon were resected. The pathology report (S63-4503) was of partially differentiated adenocarcinoma of the colon.

In October, 1967, she was admitted to Cincinnati General Hospital for pain in the left hip and leg. X-rays of the pelvis showed sclerosis of the medial aspect of the left ilium compatible with metastatic neoplasm. Because of this lesion, the area was treated with supervoltage therapy. The left posterior pelvis was treated to a total skin dose of 4556 R from October 27, 1967 to November 14, 1967, and the anterior LUQ received a total skin dose of 2856 R from December 13, 1967 to December 29, 1967.

The patient was shammed on February 5, 1968 and treated on February 6, 1968, with 300 rad midline tissue dose (435 R midline air exposure) of partial irradiation to the lower body. She experienced no adverse side effects.

The remainder of her hospital stay she followed a continual downhill course and expired March 11, 1968, 34 days post PBR.

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13. ABSTRACT <p>In this report there are included biochemical studies of deoxycytidine, immunology, psychological and psychiatric factors, clinical observation of autologous marrow infusion and computer analysis of hematological data (U).</p> <p>Deoxycytidine: Urinary deoxycytidine is found to be increased after x-radiation in man (U).</p> <p>Immunology: Efforts thus far expended in learning to grow and purify bacteriophage. Those will be used as antigens in irradiated patients (U).</p> <p>Psychological and psychiatric factors: A review of the testing procedures utilized during the pre-irradiation and post-irradiation periods is given along with the results of these tests (U).</p> <p>Autologous marrow infusion: Patients receiving 200 rads of total body radiation received autologous marrow infusion. Trypan blue was used to determine viability of marrow cells (U).</p> <p>Computer analysis of hematological data: Discriminant function analysis is used to distinguish between groups given high and low radiation doses. Parameters evaluated were the cellular elements of the blood (U).</p>		

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